

TESTING A SCREENING TEST

In *Bandolier* 3 the criteria used to test a test were discussed. When testing a new test against an established diagnostic test or procedure, improvements in sensitivity, specificity and predictive value are sought, as well as cost and patient acceptability. These simple criteria need to be applied to all new screening tests, and to many screening tests presently in use.

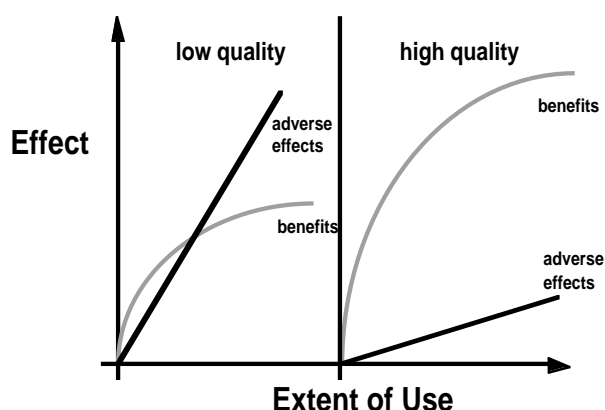
Screening - a major problem for the nineties

Screening tests are relatively inexpensive when compared with the treatment of chronic disease or major operations, but the total expense of all screening programmes in the UK is considerable, probably about £500 million per annum.

No screening test should be introduced until it has been subjected to rigorous evaluation and meets strict criteria [1]. The criteria used to assess the screening test should be even stricter than those used when considering a new diagnostic test, for screening tests are, by definition, provided for healthy populations. There are quite different ethical contracts between the provider of screening and the healthy person invited to be screened and those which exist between the clinician and the patient who has sought help for a problem that is causing concern.

Screening tests should only be offered to the population after it has been proved that they are effective and that the resources are available to deliver a high quality service to the population as a whole. Only two or three of the twenty or so screening tests on offer to the population meet these strict criteria.

Benefits & Risks of Low & High Quality Screening



The need for high quality in screening

In a screening test the balance between adverse and beneficial effects is often fine. High quality screening is essential if benefits are to outweigh the social and financial costs of screening, particularly when it is remembered that the social cost of screening - for example, the anxiety that results from a false positive test - is borne by a healthy member of the population who will not benefit from the screening programme as an individual.

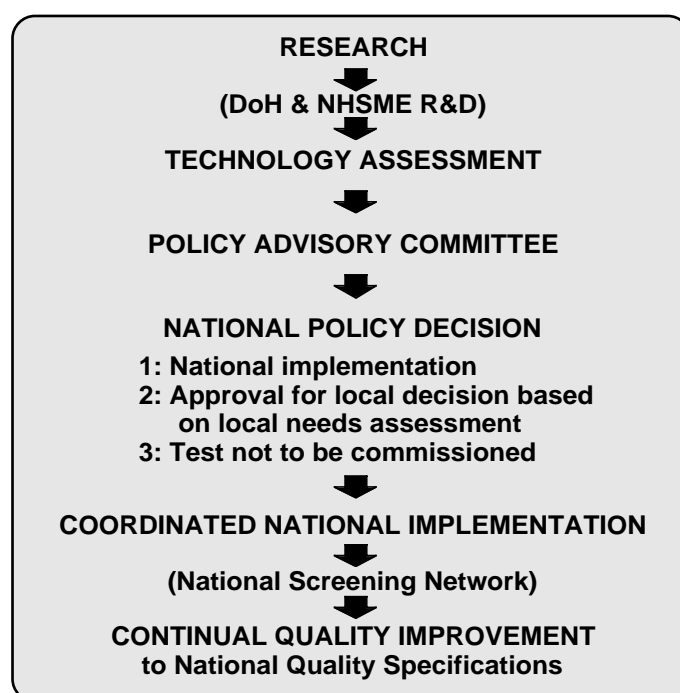
The relationship between quality and the balance between costs and benefits is shown in the figure.

No screening tests should be offered, therefore, unless there are:

- explicit quality criteria
- an information system which collects the data that allows the achievement of standards to be measured
- a system for taking managerial action if standards are not being met

The Chief Medical Officer's national screening initiative

The new Journal of Medical Screening has been published by BMJ Publications, and at a conference to launch this journal the Chief Medical Officer made a major speech outlining the steps that should be taken in future to ensure that only effective screening tests which can be delivered at high quality are offered to the public. The system proposed is:



Four types of screening test

The various screening tests that exist at present can be classified into four main groups.

- Tests whose effectiveness is unknown and which are not available to the public
- Tests of unknown effectiveness which are currently being offered to the public
- Tests of proven effectiveness which need to be introduced in a systematic and controlled way
- Tests of proven effectiveness which are being offered to the public but which need quality improvement

A strategy for tests of unknown effectiveness

The National Research and Development Strategy has identified screening as one of its main targets for action. The Standing Group on Health Technology has set up a Population Screening Panel, chaired by Dr Sheila Adam, Director of Public Health in North West Thames Regional Health Authority. The Population Screening Panel has already identified five tasks which have been classified as being of the highest priority by the Central Research and Development Committee. These are listed below.

1. Screening for colorectal cancer: to assess whether screening by flexible sigmoidoscopy once at age 55 to 60 can reduce mortality from colorectal cancer
2. Screening for stroke by identifying high blood pressure and treating it effectively: to inform NHS decision-makers about areas where policy is clear and areas where policy or further research is needed
3. Review of the management of mildly or moderately dyskaryotic cervical smears: to provide clear guidelines and informed policy regarding the effectiveness and relative cost-effectiveness of different referral and management policies for women with mildly or moderately dyskaryotic cervical smears
4. Antenatal screening for HIV: to assess the feasibility, costs and benefits of screening pregnant women for HIV in areas of high prevalence
5. Evaluation of methods of screening for Down's syndrome: to assess the costs, benefits (from the perspective of purchasers, providers and users) and effectiveness of different methods of screening in order to inform policy

There are two important points about this list of priorities:

- it covers both screening tests which are not yet available and existing screening tests
- it does not cover all the screening tests which need critical appraisal; in particular the rapid developments in genetics and molecular medicine

The Chief Medical Officer's initiative

The development of a clear programme of screening research is the first step, and a vitally important one in improving screening in England. The Chief Medical Officer,

in his major speech at the screening conference, outlined the steps that needed to be taken to ensure that decisions to implement screening resulted in high quality and effective screening programmes.

He cited the Breast Screening Programme as an example of successful screening. A number of factors were identified that led to the success of this programme, notably:

- an explicit assessment of the technology - the Forrest Report
- a clear national policy decision
- the identification of resources earmarked for screening
- strong national leadership and co-ordination
- a policy advisory committee which could monitor the impact of the policy; the Departmental Committee chaired by Professor Martin Vessey
- the development of explicit and agreed quality standards which provided a strong basis for quality assurance

The Chief Medical Officer proposed that the same approach be used to improve the quality of cervical screening. Much has been achieved in the last five years by the activities of the National Co-ordinating Network but more resources are needed for stronger national co-ordination and clearer and more explicit quality standards.

He also proposed that a National Screening Network (NSN) be set up.

The National Screening Network

The National Screening Network will seek to link the various screening programmes, both new and existing programmes, to ensure co-ordinated programme development and quality improvement.

Dr Muir Gray has been asked to act as Co-ordinator of the National Screening Network which will be part of the Chief Medical Officer's Public Health Network.

Objectives of the National Screening Network

1. To ensure that screening programmes are not introduced until a national policy decision has been made by supporting health authorities seeking to stop the piecemeal and uncoordinated implementation of screening tests as a result of local enthusiasm
2. To identify screening tests or programmes that require reappraisal of their effectiveness and appropriateness, submitting information of evidence to the Population Screening Panel of the Standing Group on Health Technology
3. To ensure that new screening programmes are introduced in a co-ordinated fashion
4. To co-ordinate and support the work of national co-ordinators of individual screening programmes to improve the effectiveness and quality of screening

Priorities for 1994/95

At the screening conference a number of priorities were identified.

- The development of criteria that can be used to assess genetic screening programmes
- The more tightly co-ordinated implementation of Down's syndrome screening to ensure that those populations covered by Down's syndrome screening are covered by a high quality and effective service
- A review of blood pressure screening
- A review of child health screening to identify which screening tests need particular consideration and review

Giving advice to those who purchase health care

The principal objectives of the National Screening Network and the Population Screening Panel will be to give advice to those who commission health services. On the basis of information currently available, it is possible to give clear and categorical advice on certain screening programmes.

- Screening for ovarian cancer should not be introduced or offered except as part of a controlled trial of its effectiveness
- Screening for carcinoma of the prostate, recently highlighted in the House of Commons debate on the early detection of cancer, should not be offered to the public unless as part of a controlled trial
- Whole population screening for raised levels of cholesterol should not be offered to the population, although about £40 million or £50 million of medication is currently being prescribed to reduce cholesterol levels as a result of haphazard and uncoordinated cholesterol testing
- Screening for abdominal aortic aneurysm should not yet be introduced as a standard screening programme

The work of the National Screening Network will be featured in future editions of *Bandolier*.

Reference:

JMG Wilson & G Jagoner. Principles and Practice of Screening for Disease. WHO 1966.

CHOLESTEROL: SCREENING & TREATMENT

The importance of cholesterol and cholesterol screening in coronary heart disease (CHD) continues to cause controversy in the pages of our most prestigious medical journals. *Bandolier* is not able to summarise all of that ongoing dispute, but does want to remind its readers of the important Effectiveness Bulletin on "Cholesterol: Screening and Treatment" published by the University of York in June 1993.

The bulletin is short (8 pages), readable and packed with useful information and cogent argument.

Cholesterol as a risk factor

CHD mortality goes up with increasing serum cholesterol. When serum cholesterol rises from 5 to 7.8 mmol/L the age-adjusted 6-year death rate is three times higher than at 5 mmol/L. Cholesterol is only one of a number of independent risk factors, including cigarette smoking, high blood pressure, diabetes, lack of exercise and obesity, all of which contribute to CHD.

Is Cholesterol a good measure of risk?

Blood cholesterol by itself is a poor predictor of individual risk of CHD. Data from large studies indicate that there is massive overlap between cholesterol concentrations in individuals who did or did not have a heart attack. Apart from those with very high cholesterol levels an individual's cholesterol value (for 98% of the population) cannot be connected with individual risk of CHD.

Are Cholesterol assays accurate enough?

Over and above the variations in blood cholesterol that occur through the day are superimposed any imprecisions and inaccuracies in the measuring system.

Most hospital biochemistry laboratories do a pretty good job, with levels of accuracy and precision which meet good practice guidelines. Desk-top analysers have a worse reputation, with levels of inaccuracy and imprecision which could mean that a GP would not in reality distinguish confidently between a patient with a value of 7.1 mmol/L (raised) and 5.3 mmol/L (not raised).

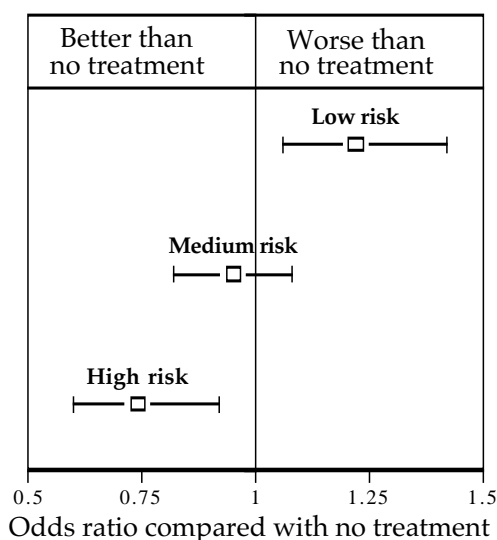
Are Cholesterol lowering treatments effective?

Cholesterol lowering is effective in reducing overall mortality in a small group of patients at high overall risk of CHD death. Few people identified purely on the basis of cholesterol levels will benefit from treatment.

A meta-analysis which included all randomised controlled single factor trials of cholesterol lowering treatment with at least six months follow up, and in which at least one death occurred, showed that treatment was better than no treatment only in those with a very high overall risk of CHD death (>50 deaths per 1000 person years). There was no benefit for those with medium risk (10-50 per 1000); more people with lower CHD risk (<10 per 1000) died taking therapy.

The only people likely to benefit from cholesterol lowering are those with over a 3% chance of dying from a CHD event in the next year. These will have combinations of risk factors, such as men with ischaemic changes, who smoke, have high blood pressure and high cholesterol.

Cholesterol lowering treatments
in groups with different CHD risk

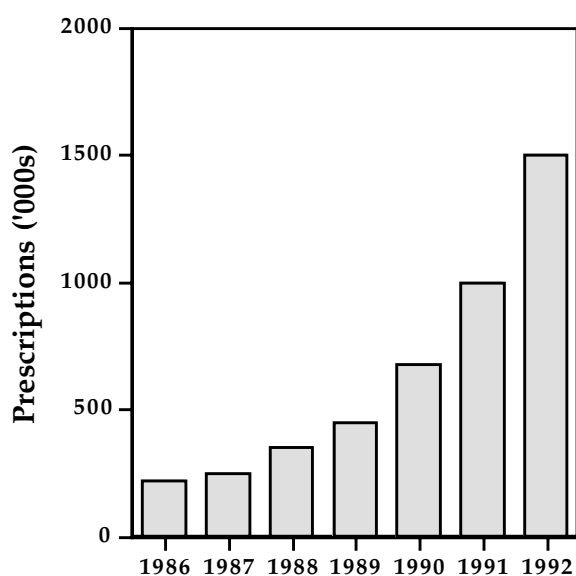


What are the cost implications?

Prescribing of cholesterol lowering drugs in primary care cost £34 million in 1992, and the number of prescriptions is increasing at about 20% per year. The cost per patient is about £400 for both drug treatment and monitoring over one year.

About 120,000 people are estimated to be on treatment, increasing by 27,000 or more each year. The potential for cost escalation is very large, not only because of increases in prescribing, but also because patients may be switched from fibrins to HMG CoA reductase drugs (statins) which are more expensive; the full cost implication of the latter is nearly £20 million a year.

Cholesterol lowering drug prescriptions



Implications for health care?

Cholesterol screening will not make a contribution to the lowering of overall mortality rates and should be actively discouraged. Therapy should be targeted at those patients with the highest overall CHD risk.

The Health of the Nation target for reduction of CHD by the year 2000 is 40%. Unstructured cholesterol screening and treatment will not be effective in helping to achieve that goal.

Reference:

Effective Health Care. Cholesterol: Screening and Treatment. June 1993. Available from Effective Health Care, 30 Hyde Terrace, Leeds LS2 9LN.

DRUG SCREENING IN THE USA

Drug screening in the USA began in the 1970s as an attempt to curb the spread of drug abuse in the US military forces in Vietnam; the Navy started screening after an accident on the carrier Nimitz revealed that a number of sailors and airmen were taking mind-altering drugs. In 1986 all Federal government employees were included in mandated drug screening programs. By 1994 drug screening had been extended to all workers in industries regulated by the Federal government (nuclear energy, petroleum, aviation, railroad, maritime and road transportation etc.). It is estimated that 50-75% of medium to large US companies have employee drug testing programs.

Urine as the specimen of choice

The best specimen for therapeutic drug monitoring or for forensic toxicology is blood. It was evident that it would be impractical to take blood from millions of workers to be covered by the drug screening program. Taking urine samples is less invasive.

The goal of the program was to determine a history of drug use rather than to confirm drug intoxication. The presence of low levels of urine metabolites of drugs of abuse can indicate exposure which occurred days or weeks before, even when there is no question of present drug intoxication or fitness for duty.

The designation of urine as the only acceptable specimen for drug screening was made law in 1988 [1]. In addition to strict rules for collection and preservation of unadulterated urine specimens, testing protocols were mandated. Urine may be used for cannabinoids, opiates, cocaine, amphetamines and PCP only. The initial test must be an immunoassay followed by confirmation of positive specimens by GC/MS.

Using urine specimens focused everyone on urinary metabolites and set drug cut-off concentrations appropriate for urine only. They forgot about active drug and active metabolites found in blood, sweat, saliva or hair. Methods now available tend to conform to the characteristics of en-

zyme immunoassay tests used by the US military in the 1970s; and many other exciting developments have been slowed because of the US concentration on urine.

Laboratory accreditation for drug screening

The HHS Mandated Guidelines [1] dictate specimen choice, collection, testing procedures and interpretation of results. All laboratories which test employees covered by the Federal drug screening program must be accredited as following these guidelines. Most private industrial drug screening programs have adopted these same requirements. Accreditation is achieved by on-site inspection every six months and a proficiency testing program consisting of ten urine specimens sent three times a year. A laboratory which gets a false positive result loses its accreditation.

Over 90 laboratories across the USA currently maintain accreditation in this program. Review and grading of both inspections and proficiency tests by a central group ensures that any urine drug screening test performed anywhere in the USA will follow the same procedures and produce the same results. This is perceived by the public as ensuring fairness in the drug screening program.

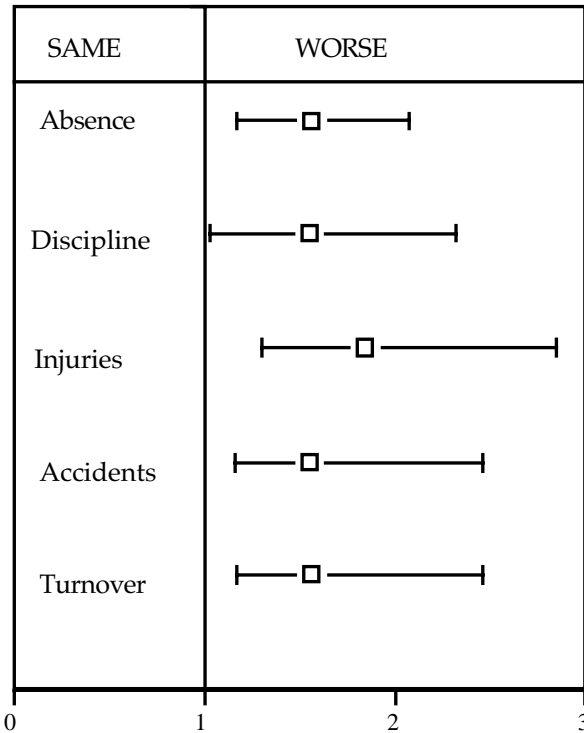
Cost effectiveness depends on prevalence

Drug screening has invaded the privacy of workers not charged with any crime. Drug screening costs millions in laboratory test fees and has narrowed the availability and acceptability of drug tests used in the USA. Is it worth the cost?

The effect of a pre-employment urine drug screening program for the US Postal Service has been published in JAMA [2,3]. It involved 2537 workers employed in Boston whose employment history was followed for about 400 days. The results of drug screening were blind to the management. Specific end points were time to termination (dismissal or resignation), absence rate, time to first work-related accident and injury and time to first reported disciplinary action.

Analysed separately for marijuana, cocaine and other drug use compared with employees who had negative drug tests on the pre employment screen, there were significant differences. Drug users overall had an absenteeism rate twice as high as non drug users. Marijuana users left employment earlier, had more accidents and injuries, had a poorer disciplinary record and more absences (all statistically significant; see below). Cocaine users had significantly more injuries and greater absence, while other drug users had a significantly worse disciplinary record.

The cost benefit analysis showed that a positive effectiveness ratio depends upon the prevalence of drug use in the subject population. For the US Postal Service this occurs for a population which has a prevalence of drug abuse of 5% or higher. Cost saving was \$162 per applicant hired over one year but industries with high accident costs could benefit more.

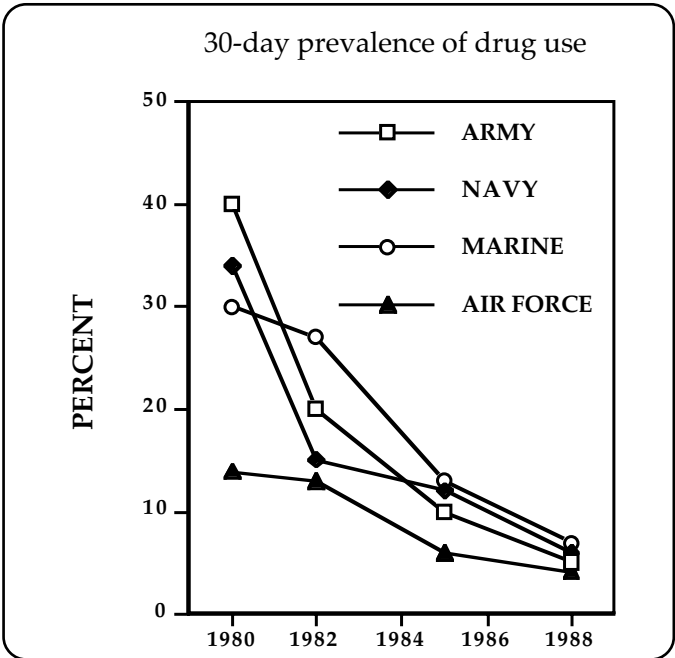


Odds ratio (95% CI) for marijuana users relative to non users

Before the start of drug screening in the US military, surveys showed a prevalence of drug use of 47% [4]. When random testing was begun, the positive rate was 22%, a figure which steadily declined every year to 2.5% after six years of testing [4] and to less than 1% today.

Some of the apparent decline has been offset by the use of drugs which are not detected in the screening tests. For example, the young recruits substituted MDMA (Ecstasy) for cannabis, LSD for PCP and pethidine or fentanyl for heroin.

The program has been able to follow drug abuse patterns by adding tests, changing the frequency of screening tests and the cut-offs used. For instance, screening for LSD was instituted in 1990 in the Navy when it was found that LSD was being smuggled aboard ships at sea. The US Navy has largely achieved its goal for drug abuse, "Not on my watch, not on my ship, not in my Navy!" The Federally mandated



employee testing has not shown similar flexibility since its technical requirements are mandated by law rather than by executive command. While drug screening positive rates in the military are constant at about 1-2% positive results (probably lower than prevalence in the population in general), pre-employment testing has shown a lowering of positive rates from 17% to about 10%. This may, however, be a simple reflection of greater unemployment among older workers in recent years rather than deterrent effects of drug testing; most drug use is in the population of 18-30 year old, non-Caucasian males.

Private sector employee drug testing programs have been shown to improve workplace safety and employee productivity, as well as to decrease health benefits costs, absenteeism and employee turnover [5].

Conclusion

In selected populations prone to drug use (prevalence greater than 5%) random urine drug screening can identify incorrigible drug users and deter others from the abuse of drugs. This results in greater public safety and reduced health care costs.

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References:

- 1: Mandatory Guidelines for Federal Workplace Testing, Department of Health and Human Services. Federal Register 1988 **53**: 11970.
- 2: Zwerling C, Ryan J, Orav EJ. The efficacy of preemployment drug screening for marijuana and cocaine in predicting employment outcome. *Journal of the American Medical Association* 1990 **264**:2639-43.
- 3: Zwerling C, Ryan J, Orav EJ. Costs and benefits of pre-employment drug screening. *Journal of the American Medical Association* 1992 **267**: 91-3.
- 4: Irving J. Drug screening experience in the military. *Clinical Chemistry* 1988 **34**: 637-40.
- 5: Sunshine I. Mandatory drug testing in the United States. *Forensic Science International* 1993 **63**: 1-7

ANTIOXIDANT THERAPY FOR RECURRENT PANCREATITIS

There is little to offer patients with recurrent pancreatitis in way of treatment. These patients suffer considerable pain, and about the only measure that will guarantee long-term pain relief is near-total pancreatectomy - which carries the penalties of malabsorption and brittle diabetes. Though the number of patients with chronic pancreatitis will be small across the UK, there may be pockets of relatively high prevalence, largely in deprived areas. These patients will consume significant amounts of health service resources - even more if near-total pancreatectomy is carried out. Any therapy which can be shown to be effective in chronic pancreatitis will therefore have an impact on healthcare provision.

Causes of pancreatitis

There is accumulating evidence that oxidant stress resulting from an excess of pro-oxidant over antioxidant has a key role in acute oedematous pancreatitis as well as painful exacerbations of chronic disease. Cytokines like platelet activation factor (PAF) have also been shown to be involved with development of the acute disease in animal models, but it is likely that the prime insult which triggers pancreatitis is oxidant stress.

Antioxidant therapy?

From this, it would seem likely that therapy with antioxidants should help to prevent pancreatitis - especially recurrent pancreatitis. A randomised, controlled, double-blind, double dummy, crossover study from the Manchester Royal Infirmary has shown this to be the case.

Twenty patients with chronic pancreatitis (8 idiopathic, 7 alcoholic and 5 idiopathic acute) entered the study in which micronutrient antioxidant therapy was compared with placebo, each for a 20-week period. Patients took six tablets of selenium bCE (Wassen International) and eight tablets of methionine (Evans Medical Ltd) in divided doses, giving a daily total of:

600 µg organic selenium 9000 IU B-carotene
0.54 g vitamin C 270 IU vitamin E
2 g methionine

Results

This was a thorough and detailed study. The bare-bones of the results were that while six patients had an attack while on placebo, not one had an attack while on active medication. Pain scores were significantly lower on active treatment than on placebo and at baseline. The blood concentrations of a free radical 'marker' - the percentage molar ratio of 9,11-linoleic acid to 9,12-linoleic acid - were elevated at baseline and in patients on placebo, but werenormalised by active treatment.

Benefits and costs

Treatment would entail a maximum cost of about £15 a month (1990 prices), with possibly a 50% reduction after six months. This financial outlay is small compared with the cost in terms of the mortality, morbidity, narcotic use, malnutrition and brittle diabetes of near-total pancreatectomy.

Reference:

S Uden et al. Antioxidant therapy for recurrent pancreatitis: placebo controlled trial. *Alimentary Pharmacology and Therapeutics* 1990 **4**: 357-71.